Uncertainties Article

Does the addition of mesh improve outcomes in implant-based breast reconstruction after mastectomy for breast cancer?

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Background

Of the 55,000 women diagnosed with breast cancer[1] each year, over 40% will require a mastectomy[2] as primary surgical treatment. In efforts to optimise quality of life and outcomes, the National Institute for Health and Care Excellence (NICE) recommend offering immediate breast reconstruction[3]. In the UK[4] and US[5], implant-based breast reconstruction (IBBR) is the most commonly-performed technique.

The earliest approach to IBBR was to place the implant directly under the skin flaps in a subcutaneous position. This was abandoned because of unacceptably high complication rates[6] and instead, the implant is usually placed in a pocket under the pectoralis major muscle. This generally requires a two-stage approach as the initial pocket is not large enough to accommodate a fixed-volume implant so a tissue-expander is placed as a first stage. Multiple expansions (by injecting fluid percutaneously) are required until the desired size is achieved. The expander is then replaced by a fixed-volume implant at a second operation. This technique is safe, but time-consuming and uncomfortable.

The introduction of biological and synthetic meshes to augment the submuscular pocket has a major impact on the practice of IBBR. The mesh can be used as a sling between the lower edge of pectoralis muscle and the chest wall to provide coverage for the lower pole of the implant. This creates a much bigger submuscular pocket (figure 1) and allows a single-stage procedure to be performed with the definitive and right sized implant placed at the time of mastectomy. It is thought that cosmetic outcomes are improved due to better lower pole projection and improved control of the inframammary fold which creates a more ptotic natural-looking result. A wide range of biological (e.g. acellular dermal matrix, ADM) and synthetic (e.g titanium coated polypropylene) meshes are available. These differ in cost (£300 to £2000) and in the absence of comparative evidence, usage is currently dependent on surgeon preference.

Recently, practice has evolved. Surgeons may place the implant, fully or partially wrapped in mesh, on top of the pectoralis muscle in a subcutaneous position (figure 1). It is suggested that the subcutaneous technique may reduce post-operative pain as the muscle is not disturbed. Implant 'animation', the distressing upwards movement of the implant that is seen when the chest muscles contract in standard submuscular techniques is also avoided[6].

It is unclear, however, whether mesh-assisted procedures are a safe alternative to traditional IBBR techniques and if patient-reported and cosmetic outcomes are improved when mesh is used. It is unclear which type of mesh (biological or synthetic) should be used. There is also uncertainty about the best position for the implant when a mesh is used (under the skin or under the muscle).

What is the evidence of uncertainty?

We searched PubMed, the Cochrane Library and the clinicaltrials.gov databases to identify published and ongoing randomised clinical trials (RCTs) and systematic reviews that evaluated mesh in women undergoing IBBR following mastectomy for breast cancer or risk-reduction.

Mesh vs. no mesh

A 2015 systematic review evaluated the published evidence for ADM in IBBR[7]. This included 8 systematic reviews; 1 RCT; 40 non-randomised comparative studies and 20 case-series. The review concluded that current evidence was limited, and further research was required but no meta-analysis was performed due to the heterogeneity of the included studies. A more recent systematic review[8 9] included 28 non-randomised studies and 23 case-series reporting the outcomes of biological and synthetic meshes. Several meta-analyses were performed to compare overall complications and specific clinical outcomes including implant loss, infection and capsular contracture in patients undergoing IBBR with and without mesh. Pooled analysis suggested a higher rate of infection in the mesh-assisted group (risk ratio 1.55, 95% confidence intervals 1.17-2.05) but no other significant

differences in complications when mesh was used, but the quality of the included studies was low[8]. It concluded that data, in particular relating to health-related quality of life and oncological outcomes were lacking and that RCTs were 'urgently needed'[9].

Since the completion of these reviews, a multicentre Dutch RCT comparing quality of life, safety and cosmetic outcomes in single-stage direct-to-implant IBBR with ADM and traditional two-stage expander-implant reconstruction has reported[10] (table 1). To date, only safety data at one year are published but patients in the ADM group experienced significantly more surgical complications (odds ratio 3.46, 95% confidence interval 1.39-8.61), complications requiring re-operation (odds ratio 3.69, 95% confidence interval 1.31-10.42) and a higher incidence of reconstructive failure (odds ratio 16.82, 95% confidence interval 2.44-115.94) than those undergoing two-stage expander-implant reconstruction. While these results are concerning, the study is small (n=142) and at high risk of bias due to lack of blinding of outcome assessors. Importantly, it did not take account of the learning curve of participating surgeons[11] which has been shown to significantly impact on surgical complications in ADM-assisted IBBR[12].

A multicentre prospective North American cohort study[13] has recently compared complications and patient-reported outcomes in 1297 women undergoing two-stage IBBR with and without ADM. Complications were defined as adverse, surgery-related post-operative events requiring additional treatment at 2 years following expander placement. The incidence of any complication, major complications requiring re-operation or readmission to hospital and reconstructive failure (removal of the implant) was compared between the procedure groups and patient-reported outcomes were assessed pre-operatively and at 1 week, three months, one and two years post-operatively using the validated BREAST-Q questionnaire. There were no significant differences in the clinical or patient-reported outcomes between the two groups. Although this is an interesting study that provides data on the two-stage approach, this is not standard practice in the UK. There also remains the need to evaluate it within the context of a randomised study.

Type of mesh: biological or synthetic?

The 2015 systematic review[7] included nine non-randomised studies comparing different types of ADM. These were small, retrospective, mostly single-centre reports and the findings of no differences between products are of limited value

An updated literature review has identified two small single-centre RCTs comparing complications of different human ADMs[14 15] and have demonstrated no significant differences in outcomes between different products (table 1). These studies were not reported in sufficient detail for the risk of bias to be formally assessed, but as the trials were largely explanatory, the results are unlikely to be generalisable. A third small pilot RCT compared biological and synthetic meshes[16]. This study compared cosmetic outcomes using panel photographic assessment, complications and quality of life using the EORTC QLQ C30 and BR23 questionnaires in patients receiving biological and synthetic mesh. There were no significant differences in cosmetic outcome and overall complications between the patient groups, but patients in the ADM group experienced significantly higher rates of implant loss than those undergoing IBBR with synthetic mesh (n=7 vs. n=2, P<0.0001). Patients in the ADM group also reported more post-operative pain, more fatigue and more disruption to their family life than those in the synthetic mesh group. Although reported as a 'pilot' trial, this study is a small trial that is insufficiently well-designed to look at the target different between the treatment groups[17]. No primary outcome or power calculation are reported and there are insufficient details to allow the risk of bias to be formally assessed. This study therefore represents very low quality evidence the results of which cannot be relied upon (table 1).

Subcutaneous vs. submuscular implant reconstruction with mesh

Our updated search did not identify any RCTs or systematic reviews in this field. Just one narrative review was found[6]. This includes case-series with few studies directly comparing submuscular and subcutaneous techniques.

Is ongoing research likely to provide relevant evidence?

Searches of ClinicalTrials.gov; the ISRCTN registry and the Cochrane Library identified several small ongoing randomised trials; two multicentre studies comparing two-stage expander-implant and single-stage direct-to-implant reconstruction with ADM in Europe (NCT02061527,n=120) and Canada (NCT00956384,n=189) and five further studies comparing meshes; three comparing human (NCT03145337;NCT02891759) and non-human ADMs (NCT02521623;n=60) and three comparing biological and synthetic mesh in submuscular (NCT02985073;n=40) and subcutaneous (NCT02830685; NCT02831426) IBBR. A single small study (NCT03143335) was identified comparing subcutaneous and subpectoral techniques.

While these trials will add to the evidence-base, they are unlikely to be sufficiently large or pragmatic to definitely determine whether mesh is safe or if it improves patient-reported and cosmetic outcomes in IBBR; which mesh should be used or where the implant should be placed.

The iBRA study (ISRCTN37664281) is a non-randomised prospective multicentre cohort study which aims to inform the feasibility, design and conduct of a pragmatic RCT in IBBR[18]. iBRA will provide important data for hypothesis generation and it will inform an efficient and acceptable trial design. It is also serving as an important process of establishing networks and demonstrating how plastic and breast surgeons can work together.

What should we do in light of this uncertainty?

In light of the lack of evidence and recent issues with other mesh-based procedures[19], surgeons and specialist nurses involved in breast reconstruction decision-making should ensure that patients are fully-informed that there is limited short and long-term safety and patient-reported outcome data for mesh-assisted IBBR and that surgeons may have limited experience with the technique. As large numbers of women are electing to undergo these

procedures, the degree to this information is currently shared with patients is unknown, raising questions about the quality of information provision and informed consent.

Published guidelines[20 21] are largely based on poor-quality evidence and expert opinion but offer sensible advice regarding current best practice. The American Society of Plastic Surgeons recommend that mesh use should be considered on a per-patient basis[20]. Careful patient selection and performing mesh-assisted IBBR with caution in high-risk groups (such as current smokers, patients who have had previous breast radiotherapy, and those with a high BMI) is recommended by the UK professional associations, the Association of Breast Surgery (ABS) and the British Association of Plastic, Reconstructive and Aesthetic Surgeons[21] together with robust prospective audit of surgical outcomes to generate data to support practice.

New techniques and devices in breast reconstruction require evaluation. Surgeons need to embrace the concept of 'no innovation without evaluation' and commit to only performing new techniques within the context of well-designed protocolled early-phase evaluation studies or registries using standardised outcomes measures. Equally it is possible that governance structures for surgical innovation need to change.

RCTs in IBBR are urgently-needed and notoriously challenging but careful feasibility work may be the key to successful future trials. Patients and the reconstructive community need to work together to design and conduct multicentre, pragmatic studies that will provide much-needed evidence to determine the best and most cost-effective approach to IBBR.

Recommendations for further research
Population: Women aged 16 or over undergoing mastectomy for breast cancer or risk-reduction electing to undergo immediate implant-based breast reconstruction
Intervention and comparisons: The key question is whether ADM improves the outcome of implant-based breast reconstruction but there is also a need to determine which type of

mesh and where the implant should be placed. It may be possible to address the questions within a single trial with an adaptive or factorial design.

i) Single-stage direct-to-implant reconstruction with mesh vs standard two-stage expander-implant reconstruction

ii) Biological vs synthetic mesh

iii) Subcutaneous vs submuscular implant reconstruction with mesh

Outcome: Patient-centred outcomes including patient satisfaction although safety outcomes such as rates of implant loss will be important, and the use of the breast reconstruction core outcome set[22] would be recommended. Adequate follow up and appropriate timing of outcome assessment will essential to understand the final cosmetic result achieved and robust economic evaluation will be an important component of any future trial.

What you need to know

Implant-based breast reconstruction is the most commonly performed procedure in the UK and US

The use of biological and synthetic meshes in implant-based reconstruction has become standard care, but there is limited high-quality evidence to support their safety or effectiveness.

Surgeons performing breast reconstruction need to work together to generate evidence to support practice.

How patients were involved in the creation of this article

A patient advocate is a co-author of this article and patients are involved on the steering group of our ongoing IBBR studies.

They expressed concerns that patients are unaware of the degree of uncertainty surrounding the use of mesh and that it is difficult for patients to get clear advice on what approach would be right for them.

We have ensured that the 'what patients need to know' box includes questions for patients to ask their surgeon which may help them make more informed decisions about their options.

What patients need to know

Surgeons offering mesh-assisted implant-based breast reconstruction should explain to patients that although we believe that mesh may improve patient satisfaction and cosmetic outcome, there is no good published research to support this.

Surgeons should explain that the short-term complications of mesh-assisted procedures may be higher than traditional implant-reconstruction and that we don't currently understand the long-term outcomes of mesh-procedures including the need for further surgery over time.

Surgeons should be able to share their personal complication rates in particular how many patients need a second operation for complications and how many patients need their implant removed, why this may be needed and when it may occur to help patients make more informed decisions about surgery.

Surgeons should be transparent and honest if they are trying a new technique such as placing the implant under the skin for the first time and allow patients to decide whether or not they would like to choose this option.

Surgeons should encourage patients electing to undergo mesh-assisted procedures to take part in research studies to address some of these uncertainties.

Education into practice

Do you mention the lack of evidence for the use of mesh in your discussions with patients considering implant-based breast reconstruction?

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SP and JMB identified the topic; SP conducted the review and wrote the first draft of the manuscript; SP, MM and JMB critically reviewed and revised the manuscript and all authors approved submission. SP is the guarantor.

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Table 1 – Summary of randomised clinical trials evaluating mesh use in implant-based breast reconstruction

RCTs comparing implant-based breast reconstruction with and without mesh							
Study	**Sample size**	**Intervention**	**Comparison**	**Outcomes assessed**	**Main findings**	**Quality of evidence[a]**	**Uncertainty**
McCarthy et al, 2012	69	2 stage expander-implant reconstruction with human ADM (AlloDerm) n=33	Standard 2 stage expander-implant reconstruction n=36	i. Pain using BREAST-Q Physical well-being Chest and Upper Body Scale and VAS post-operatively and during expansion phase ii. Rate of tissue expansion	No differences in pain post-operatively or during the expansion period. No differences in rate of post-operative expansion	Moderate	Underpowered - Study stopped by Data Safety Monitoring Board due to concerns about recruitment. Use of human ADM in 2 stage expander-implant reconstruction does not reflect UK practice
Dikmans et al, 2016	142	Single-stage direct to implant reconstruction with porcine ADM (Strattice) n=59	Standard 2 stage expander-implant reconstruction n=62	i. HRQL assessed using the BREAST-Q and EQ-5D at 1 year ii. Safety – adverse events classified using CTCAE criteria at 1 year iii. Aesthetic outcomes based on photographs at 1 year	Significantly higher rates of surgical complications (OR 3.46, 95% CI 1.39-8.61); re-operation (OR 3.69, 95% CI 1.31-10.42) and removal of implant (OR 16.82, 95% CI 2.44-115.94) in patients undergoing single stage reconstruction with ADM compared with 2 stage expander-implant procedures without ADM. HRQL and aesthetic outcomes not reported.	Very low	Very selected patient population (non-smokers, BMI<30, no post-mastectomy radiotherapy, small breasts) High risk of bias due to lack of blinding Failed to account for surgeons' learning curve with new technique Two surgeon model (oncologic surgeon performing mastectomy and plastic surgeon performing reconstruction) not consistent with UK practice.
RCTs comparing different types of mesh							
Study	**Sample size**	**Intervention**	**Comparison**	**Outcomes assessed**	**Main findings**	**Quality of evidence[a]**	**Uncertainty**
Mendenhall et al, 2015	116	2 stage expander-implant reconstruction with human ADM (DermaMatrix) n=59	2 stage expander-implant reconstruction with human ADM (AlloDerm) n=57	i. Incidence and grade of complications ii. Expander dynamics iii. Biointegration of ADM	No difference in overall complications (OR 1.24, 95% CI 0.64-2.40) or grade of complications (OR 1.33, 95% CI 0.75-2.35) between treatment groups. AlloDerm resulted in less time to complete expansion (42 vs 72 days, p<0.001).	Low	All procedures performed by single surgeon so not generalisable. High risk of bias due to method of allocation concealment (sealed envelopes). No reported blinding of outcome assessors Use of human ADM in 2 stage expander-implant reconstruction does not reflect UK practice
Gschwantler-Kaulich et al, 2016	48	Single stage direct to implant with porcine ADM (Protexa) n=23	Single stage direct to implant with synthetic mesh (TiLOOP) n=25	i. Cosmetic outcome assessed from photographs ii. Complications iii. HRQL assessed using EORTC QLQ C30 and BR23	No significant difference in overall complications between patient groups (31.3% ADM, 24.0% TiLOOP, p=0.19) but significantly higher rate of implant loss and reconstructive failure in the ADM group (30.4% vs 7.7%, p<0.0001). Patients in ADM group reported significantly more arm pain (48% vs. 24%, p=0.04) and fatigue (35% vs 12%, p=0.03) at the first post-operative visit and a more affected family life (17% vs 0%, p=0.02) and less sexual interest (17% vs 48%) at 6 months following reconstruction. There was no difference in cosmetic outcome.	Very low	Reported as 'pilot' RCT but no feasibility endpoints assessed. Underpowered trial. No primary endpoint identified; no power calculation performed Insufficient details reported to assess risk of bias. HRQL instruments not validated in BR population ADM assessed not routinely used in UK
Hinchcliff et al, 2017	30	2 stage expander-implant reconstruction with human ADM (AlloMaxTM) n=15	2 stage expander-implant reconstruction with human ADM (AlloDerm) n=15	i. Complication rate ii. Patient satisfaction at 1 year using BRECON-31 questionnaire	No significant difference in complications between patient groups at 30 days or following implant exchange	Very low	All procedures performed by single surgeon so not generalisable. Very small sample size Insufficient details reported to formally assess risk of bias Use of human ADM in 2 stage expander-implant reconstruction does not reflect UK practice

[a]using GRADE; ADM – acellular dermal matrix; CI – confidence interval; CTCAE – Common Terminology Criteria for Adverse Events (version 4.0), EORTC – European Organisation for Research and Treatment of Cancer; HRQL – health-related quality of life; OR – odds ratio; UK – United Kingdom, VAS – visual analogue scale.